CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761164Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 128190

MEETING PRELIMINARY COMMENTS

Michelle Carpenter, JD
Executive Director, Regulatory Affairs
Bioverativ USA, Inc.
225 Second Avenue
Waltham, MA 02451

Dear Ms. Carpenter:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sutimlimab.

We also refer to your September 5, 2019, correspondence, received September 5, 2019, requesting a meeting to discuss the final components of their BLA and review their topline data from the Phase 3 pivotal (CARDINAL) trial.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Rosa Lee-Alonzo, PharmD
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

ENCLOSURE:

- Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Breakthrough Therapy - Other

Meeting Date and Time: November 6, 2019
Meeting Location: FDA White Oak Building 22, Room 1421

Application Number: IND 128190
Product Name: sutimlimab
Indication: cold agglutinin disease
Sponsor Name: Bioverativ USA Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 6, 2019; 1:00 – 2:00 PM EST; White Oak Building 22 Room 1421 between Sponsor and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Bioverativ USA submitted a Breakthrough Therapy Other meeting to discuss the final components of their BLA and review their topline data from the Phase 3 pivotal (CARDINAL) trial. The Sponsor has submitted their first portion of their BLA containing nonclinical information in September 2019 for sutimlimab for the treatment of cold

agglutinin disease. The remaining components are anticipated to be submitted in December 2019.

Sutimlimab (BIVV009) is a humanized IgG4 monoclonal antibody that works by targeting the classical complement pathway (CP) specific serine protease, complement component 1 (C1), s subcomponent (C1s; EC 3.4.21.42).

Sutimlimab was granted breakthrough therapy designation for cold agglutinin disease in May 2017 and orphan drug designation in July 2016 for auto-immune hemolytic anemia. A previous Pre-BLA meeting was held on July 24th, 2019.

2.0 DISCUSSION

2.1. Clinical (Safety and Efficacy)

Question 1: *Does the Agency concur that topline results of the CARDINAL study meet the agreed upon safety and efficacy requirements to enable review of the BLA?*

FDA Response to Question 1:
Yes. Based on the topline data submitted, your safety and efficacy data appear to support an Agency review of a BLA for sutimlimab for the proposed indication.

Additional Clinical Comments:

Describe the median hemoglobin level and range for the patients enrolled in the trial. We also note that the median number of transfusions in the last 6 months was 2 (range 1-19) which appears to be a smaller number compared to the breakthrough therapy population and thus the magnitude of change in transfusions is smaller. Ultimately, this will be a review issue.

Comment on the duration of response for the increase in hemoglobin greater than or equally to 2 grams/dL from baseline. Also, describe whether there is any rebound anemia in patients who come off of study drug.

For the patients who are considered non-responders, describe the median increase in hemoglobin. Were any of the non-responders patients who received transfusions in the prior 6 months.

Please include the following information in the submission of the BLA:

- Detailed patient narratives for all the patients
- Lattice plot for the primary endpoint of hemoglobin levels over time in the patient profiles for all patients.

2.2. Multidisciplinary (Immunogenicity data)

Question 2: *Does the Agency agree that the Sponsor's current proposal for immunogenicity data in the initial BLA filing would be adequate to support review of the BLA and inform the benefit-risk evaluation of sutimlimab for the target indication?*

FDA Response to Question 2:
The current proposal for immunogenicity data may be sufficient for the initial BLA filing. The adequacy of the data to inform the immunogenicity risk of sutimlimab and appropriate labeling will be a review issue. Your analysis should include the potential impact of immunogenicity on efficacy in addition to PK, PD, and safety. Complete and include the tables (Table 1 (bioanalytical method life cycle information) and Tables 2a-b (summary method performance of each bioanalytical method)) in your 351(a BLA submission to provide the information regarding the bioanalytical methods for pharmacokinetic and/or immunogenicity assessments used in pivotal clinical pharmacology studies and it's life-cycle information pertaining to the submission. Do not delete any rows from the tables. We recommend that these tables be included as an Appendix in the Summary of Biopharmaceutics located in eCTD 2.7.1. In addition to including in the Appendix, we request you also submit both tables in docx format. Include any other additional bioanalytical information that might be relevant for review in your BLA submission. Finally, refer to additional clinical pharmacology comments.

Table 1. Summary life cycle information of bioanalytical method(s) used in submission of BLA xxxxxx to measure analyte X in matrix

	Method validation #1	Method validation #2	Clinical Study x	Clinical Studies y-z
Analyte	Drug name	Drug x, Drug y	Drug x, and Drug y	Drug x, Drug z
Validation type	Full	Partial validation of method xx	NA	NA
• CTD ref #	Ref # in eCTD	x0000.0xxxxxxx	x0000.0xxxxxxx	x0000.0xxxxxxx
• method ID • BA site	Method ID xx (version)	SOP xxxx or Method xxx (v 1.0)	SOP xxxx or Method xxx (v 1.0)	SOP xxxx or Method xxx (v 1.0)
	Name of BA test facility	US Lab 1	US lab 1	Other lab
• Matrix	Serum/ Plasma/Urine/ whole blood			
• Platform	LC/MS, ELISA, ECL			
• Format	A validated sandwich format using x as capture and y as detection, a bridging format using z as both capture and detection, competitive assay using x as a capture and b as a competitor			
Stock reference & lot (expiry)	Drug 1, lot 1	Drug 1, lot 2 Drug 2, lot 1		
Calibration range (LLOQ -ULOQ)	x- x000 ng/mL	x- x000 ng/mL	x- x000 ng/mL	x- x000 ng/mL

and levels validated	(Eg. 2, 5, 50, 250, 1000, 1500, 2000 ng/mL)			
Matrix/ study population	Normal or x diseased serum	Normal serum	Normal serum	x Diseased population
Relevant reference and applicable report amendment (s) and links -Amendment 1 -Amendment 2				
Amendment history				

The bioanalytical method performance summary table (Table 2a) is recommended in describing PK and/or biomarker methods. Please use one method per analyte per table. This table is not applicable for anti-drug antibody methods. Do not delete any rows or columns from the table. State “not applicable” if certain rows or columns are not applicable. Include any additional bioanalytical data that may be relevant to the submission.

Table 2a. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks			
Method description			
Materials used for calibration curve & concentration			
Validated assay range			
Material used for QCs & concentration			
Minimum required dilutions (MRDs)			
Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or Product C	 x to y% x to y% x to y%	

	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
QCs performance during accuracy & precision	**<u>Cummulative accuracy (%bias) in 5 QCs</u>** QCs: Product A Product B and/or Product C	 x to y% x to y% x to y%	
	<u>Inter-batch %CV</u> QCs: Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
	<u>Total error</u> QCs: Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		
Dilution linearity & hook effect	Describe data here		
Bench-top/process stability	Describe data here Product A Product B and/or Product C		
Freeze-Thaw stability	Describe data here Product A Product B and/or Product C		
Long-term storage	Describe data here Product A Product B and/or Product C		
Parallelism	Describe data here		
Carry over	Describe data here		
Method performance in study number (In addition to the report name, also provide hyperlink to the report)			
Materials used for calibration curve & QC			
Assay passing rate	(including incurred sample reanalysis (ISR))		
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV		

QC performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)	
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	
Study sample analysis/ stability	Describe storage stability coverage for standard/QC and samples	

If the method above was modified, describe the modification(s) and cross-validation results, with any additional information in Table 2b below.

Table 2b. Summary of method [x] modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink			
Changes in method			
New validated assay range if any			
Validation parameters	**Cross-validation performance**		**Source location**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	x to y%	
	Inter-batch %CV	≤ x%	
	Percent total error (TE)	≤ x%	
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters			

From immunogenicity assay perspective, we acknowledge that you are developing an improved anti-drug antibody (ADA) immunogenicity assay for your Cardinal phase 3 clinical study to improve assay drug tolerance and to prevent target interference with C1s. We remind you that your new immunogenicity assay should be fully validated with multi-tiered testing approach (e.g., ADA screening assay, confirmatory assay, titering assay, neutralizing assay etc.) in accordance to the Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019).

2.3. Regulatory/General

Question 3: *Does the Agency plan to convene an Advisory Committee Meeting during the review of the sutimlimab BLA?*

FDA Response to Question 3:
The final determination regarding an Advisory Committee Meeting will be made after filing.

Question 4: *Does the Agency expect the Sponsor to meet for an Application Orientation meeting to discuss key aspects of the application following submission of the final components of the sutimlimab BLA?*

FDA Response to Question 4:
Yes, the agency recommends that the Applicant conduct an Application Orientation Meeting and a technical walk-through. This meeting will be scheduled after the complete application is received. See guidance below:

General Advice for Application Orientation Meetings

FDA may hold an Application Orientation Meeting (AOM) with the Applicant following submission of a new NDA, original BLA, or efficacy supplement, for purposes of orienting the review team to the content and format of the application. The meeting is generally held within 45 days of application submission. Please note, individuals from CMS may be in attendance for observational purposes. Centers for Medicare and Medicaid Services (CMS) and FDA have a Memorandum of Understanding to promote information sharing. Trade secret and other confidential commercial information are protected from unauthorized disclosure.

The following advice is intended to aide you in your AOM presentation preparation. This list is not inclusive of all issues to consider, as individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your application and therefore your presentation and/or you believe that other information is relevant, adjust your presentation accordingly.

AOMs are generally one hour in length, including time for discussion and Q & A (35-40 minutes for presentation maximum, 25-20 minutes for discussion).

The AOM may be followed by a separate 30-60 minute meeting to address technical aspects of the application limited to members of the review team, including a walk-through of the datasets.

The primary focus of the AOM presentation should be the risk/benefit profile of the product (with clinical sections presented first) and highlights of other sections to follow (1-2 slides each for remaining sections).

Administrative:

1. Sponsor attendees

2. Presentation outline - list sections included in submission.

Background and Application Specifics:

3. Proposed indication(s), current indication(s) for an efficacy supplement, and dosing recommendation(s) for the proposed indication in proposed labeling

4. Risk/benefit profile for drug/biologic

5. Drug/biologic characteristics, including what makes drug/biologic unique, mechanism of action

6. Listing of major efficacy trial(s) to support application, as well as dose-finding and activity-estimating trials supporting the proposed indication and the safety assessment.

7. Statement of whether you plan to seek accelerated approval or regular approval, if accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable for trial completion and final clinical study report submission

8. Brief Regulatory history (no more than 1 slide), including the following:
   - Orphan Drug Designation, Fast Track, Breakthrough Therapy Designation
   - Foreign regulatory history: Where/when approved and for what indications, pending applications with foreign regulators, risk management plans in foreign countries
   - Key Agreements Reached/FDA Advice in FDA Interactions
     - EOP2 Meeting
     - Special Protocol Assessment: any agreements/disagreements on primary endpoints, key secondary endpoints, statistical analysis plan
     - Pre-NDA/BLA meeting
     - Other pertinent meetings/communications with FDA marking agreements/disagreements with the Agency

Summary Content of NDA/BLA/Efficacy Supplement Sections:

9. Clinical/Statistics:
   - Description of clinical trial design, including statistical analysis plan;
   - Key findings from registration trials:
     - Minimum length of follow-up

- Demographics (including region) of subjects and baseline prognostic characteristics. NOTE: For demographics, address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.
- Outcomes from primary and secondary endpoints
- Subpopulation analyses of safety and efficacy by age, sex, race, concurrent therapy, number of prior treatments, and/or region/country if applicable
- Safety findings (most frequently reported adverse events, serious adverse events) including safety findings from trials in other phases, risk mitigation strategies for adverse reactions

Present results of the following, as appropriate:

- Biomarker development for population selection (if applicable)
- Assay validation (if applicable)

120-day Safety update: Plans including how many additional patients will be included in safety update and from which studies

In absence of unique application circumstances, the following sections should be limited to 2 slides or less:

10. CMC: Manufacturing site locations, dates available for inspection, brief summary of manufacturing process, comparability of drug substance (DS) and drug product (DP) after major manufacturing changes, characterization, controls, stability, status of drug master files, any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
    - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.

11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities

12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, description/listing of PK studies, PK characteristics (metabolic pathway, metabolites, t1/2, ADME, PK in special populations, drug-drug interactions)

13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU).

14. Summary

15. Q & A

2.4. Chemistry, Manufacturing, and Controls

Question 5: *Does the Agency agree that updated labeling associated with the submission of the photostability and in-use testing reports may be submitted within 30 days of submission of the BLA?*

FDA Response to Question 5:
We recommend that you provide draft labeling including the labeling information associated with the photostability and in-use testing results in your initial BLA submission. We acknowledge the previous agreement that data on photostability and in-use testing may be submitted no later than 30 days after submission of the BLA. However, having the complete proposed labeling during initial BLA submission, even though without the supportive CMC data, will streamline the labeling review process.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS

1. Recommendation about labeling:

We recommend that the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

2. Address the following questions in the Summary of Clinical Pharmacology:
    a. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
    b. What are the exposure-response relationships for efficacy, safety and biomarkers?
    c. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
    d. What is the impact of immunogenicity on exposure, efficacy and safety?
3. Apply the following advice in preparing the clinical pharmacology sections of the original submission:

a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

- Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

d. Submit the following for the population pharmacokinetic analysis reports:

- Standard model diagnostic plots
- Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables.
- Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometrics data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

e. Submit the following information and data to support the population pharmacokinetic analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation
- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model,

and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometrics data and models submission guidelines.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

  We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

  - Updated labeling associated with the submission of the photostability and in-use testing reports

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA 761164: LATE COMPONENT - UPDATED LABELING

In addition, we note that a chemistry pre-submission meeting was held on September 26, 2019. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned

analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[4]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[5]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone

[4] http://www.fda.gov/ectd
[5] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring*

(BIMO) Inspections for CDER Submissions (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

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Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

[6] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROSA J LEE-ALONZO
11/04/2019 12:26:21 PM

IND 128190

MEETING PRELIMINARY COMMENTS

Bioverativ USA, Inc.
Attention: Michelle Carpenter, JD, RAC
Executive Director, Regulatory Affairs
6000 Shoreline Court, Suite 304
South San Francisco, CA 94080

Dear Ms. Carpenter:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sutimlimab.

We also refer to your May 29, 2019, correspondence, received May 29, 2019, requesting a meeting to gain agreement on various aspect of the planned BLA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Rosa Lee-Alonzo, PharmD
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: July 24, 2019; 9:00 – 10:00 AM EST
Meeting Location: FDA White Oak Building 22, Conference Room 1309

Application Number: IND 128190
Product Name: sutimlimab
Indication: treatment of cold agglutinin disease
Sponsor Name: Bioverativ USA, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 24, 2019; 9:00 – 10:00 AM EST; FDA White Oak Building 22, Conference Room 1309 between Sponsor and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Bioverativ requested a Pre-BLA meeting for IND 128190 sutimlimab (BIVV009) to gain agreement on various aspect of the planned BLA. They plan to submit the application by December 2019 for the proposed indication of cold agglutinin disease.

2.0 DISCUSSION

2.1. Regulatory/General

Question 1: *Does the Agency agree with the Sponsor's proposal for Rolling Review submission of the BLA? (Nonclinical – Q3 2019, Remainder – December 2019)*

FDA Response to Question 1:
Your proposed submission timeline is acceptable. Refer to the Discussion of the Content of a Complete Application under Other Important Meeting Information below. Please note that the review clock begins at the time of the final submission and receipt of a complete application.

Question 2: *Does the Agency agree that the BLA for BIVV009 for the treatment of Cold Agglutinin Disease is eligible for Priority Review?*

FDA Response to Question 2:
It is likely that your application will receive priority review designation however the final determination of priority review designation is made within 60 days of the receipt of the complete BLA.

Provide available top-line results from the CARDINAL study for the Agency.

Question 3: *Does the Agency agree with the Sponsor's proposal to participate in the pilot program and submit an Assessment Aid in the BLA?*

FDA Response to Question 3:
No. In general, assessment aids are not used for New Molecular Entity (NME) applications. Considering this is a first-in-class product for a new indication, this application is not optimal for the use of the assessment aid. It may be feasible to consider the assessment aid for a supplemental application.

Question 4: *Does the FDA agree that a PSP is not required at the time of BLA filing and that BIVV009 is exempt from the requirements set forth in PREA because of its Orphan Drug Designation status?*

FDA Response to Question 4:
Yes, we agree. Because this drug product has an orphan drug designation for cold agglutinin disease, you are exempt from the PREA requirements. However, if there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change. In addition, please see the PREA Requirements section under the Other Important Meeting Information below.

Question 5: *Does the Agency agree with the Sponsor's use of the abbreviation "CAD" for Cold Agglutinin Disease in the labeling?*

FDA Response to Question 5:
Yes, abbreviations may be used in labeling as long as they are defined at their first use in each section of the USPI (beyond the indication statement). We do not recommend use of abbreviations in the indication statements. The rationale for defining it the first time per section is that the USPI is not read like a book; readers may go to one specific section without reading other sections.

2.2. Nonclinical

Question 6: *Does the Agency agree that there are no outstanding or unresolved topics in the BIVV009 nonclinical development program, that the requirements for registration have been met, and that the planned content of the nonclinical sections of the BLA is acceptable?*

FDA Response to Question 6:
Your nonclinical package appears to support an Agency review of a BLA for sutimlimab (BIVV009) for the proposed indication.

2.3. Clinical

Question 7: *Does the Agency agree with the proposed organization of the clinical study reports outlined in Module 5 of the BLA table of contents?*

FDA Response to Question 7:
Your proposal for the presentation of efficacy data is acceptable. The summary of clinical efficacy can serve as the ISE provided that the data can be included within the space limitations of the SCE. You may include a page with a cross-reference to the summary of clinical efficacy (SCE, Module 2, section 2.7.3) in the ISE.

Question 8: *The Sponsor proposes to provide an updated cumulative listing of serious adverse events and a cumulative listing of disposition from ongoing studies through a data cut of approximately 1 month prior to the BLA submission date in the 120-day safety update report.*

Does the Agency agree with this approach?

FDA Response to Question 8:
Yes. We agree with this approach. We remind you that if this application is granted priority review, the safety data would be due at 90 days. Please clarify what the safety data cut-off date will be for the BLA and if all patients will have the 26 weeks of follow-up at the time of submission of the BLA.

Question 9: *Does the Agency concur with the presentation of key safety information from the ongoing studies BIVV009-04 and BIVV009-201 within the Summary of Clinical Safety Module 2.7.4 rather than separate progress reports in Module 5?*

FDA Response to Question 9:
Yes, we agree with your plan to include key safety information for the ongoing studies BIVV009-04 and BIVV009-201 within the Summary of Clinical Safety (SCS) in Module 2.7.4 rather than in Module 5. Module 5 of the BLA should include tables and appendices and the datasets used for the integrated safety analyses.

Question 10: *A Bioresearch Monitoring (BIMO) report is planned for submission in 5.3.5.4 for only the CARDINAL study.*

Does the Agency concur with the Sponsor's approach?

FDA Response to Question 10:
Yes, your proposal to submit BIMO data for the CARDINAL study with this initial application is acceptable.

2.4. Clinical Pharmacology

Question 11: *Does the Agency agree with the submission plan for the immunogenicity data for BIVV009?*

FDA Response to Question 11:
It is the Agency's expectation to include all the immunogenicity data from the registration trial at the time of BLA submission to allow for assessing the impact of immunogenicity on the safety and efficacy of sutimlimab for the proposed indication.

Provide the assessment of immunogenicity impact on PK, detailed analytical procedure, and the full assay validation report from the phase I studies of the current immunogenicity assay as soon as possible to the IND and prior to the BLA submission to support the validity of the immunogenicity assay results obtained from the clinical studies.

Include a justification as to why the Agency should consider allowing a late submission of the full immunogenicity data rather than including all the data at the time of the BLA submission.

Provide the detailed analytical procedure and the full assay validation report of the newly developed immunogenicity assay when you submit immunogenicity data for sutimlimab from clinical study CARDINAL.

We acknowledge that you plan to submit the currently available ADA data from studies BIVV009-01 Parts A-C, TNT-009-02, and BIVV009-05 Part B in the proposed BLA submission, based on the current assay, in an "Integrated Summary of Immunogenicity" in eCTD module 2.7.2.4. We have the following comments:

a. Ensure that this Integrated Summary of Immunogenicity contains:
    i. An immunogenicity risk assessment specific to your product
    ii. Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods used in the program
    iii. Links to method development and validation reports for the immunogenicity assays used in your clinical studies

iv. Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed
v. Summary results of immunogenicity analysis for all clinical studies that collected immunogenicity data, including the results of your correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data
vi. Traceability of drug product lots used in all your clinical studies
vii. All immunogenicity assays, that were used during clinical development and a description of which assays were used for which studies or patient groups

We strongly recommend you request a CMC-only meeting with the Agency before submitting the marketing application.

Additional Statistics comments:

In general, regarding the data standard:

- FDA requests that an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission, be prepared and submitted in the NDA/BLA. Please refer to the "Study Data Technical Conformance Guide: Technical Specifications Document," available at: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
- Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s) to ensure efficient review.
- Provide executable program code(s) with adequate document(s) to allow FDA to duplicate the analysis datasets derivation from raw datasets
- Provide the program codes [if legacy: as well as format library files] used for efficacy and safety data analysis. If the program codes use any batched code (e.g., SAS macro), please provide all necessary macro programs.
  In addition to CDISC, if you will provide legacy (non-CDISC data) and use for actual data derivation and analysis:
- If the legacy raw and analysis datasets are used to generate the study specific CSR report and listing tables, please provide all necessary program codes. e.g., if SAS is used, please provide SAS macro, SAS format library, and adequate documents to duplicate the analysis datasets derivation from raw dataset and analysis results in the CSR and USPI.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 10, 2019 communication granting this meeting, if, at the time of

submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in

eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[4]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[5]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

[4] http://www.fda.gov/ectd
[5] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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meaning.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROSA J LEE-ALONZO
07/12/2019 02:44:35 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 128190
Request Receipt Date	March 27, 2017
Product	TNT009
Indication	Primary Cold Agglutinin Disease
Drug Class/Mechanism of Action	Humanized IgG4 mAb that binds to and inhibits the classical complement pathway (CP)
Sponsor	True North Therapeutics
ODE/Division	OHOP/DHP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	May 26, 2017

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). ***Note:*** *Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Cold Agglutinin Disease is characterized by the presence of clinical symptoms related to exposure to cold, hemolytic anemia, and antibodies(most commonly IgM and rarely IgA or IgG) directed against polysaccharide antigens on red blood cell surface that are responsible for agglutination of red cells at low temperatures. Cold agglutinins are activators of the classical complement pathway leading to deposition of C3b on the surface of red blood cells. These complement coated red blood cells are phagocytosed in the liver in the process of extravascular hemolysis. This extravascular hemolysis is the primary driver of anemia in patients with cold agglutinin disease (Brodksy 2015, Shi et al 2014, Berentsen 2014). Cold agglutinin disease is categorized into either primary or secondary with primary cold agglutinin disease thought to be due to low-grade lymphoproliferative bone marrow disorders characterized by clonal

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

expansion of B-cells (Berensten et al 2006). Secondary CAD is usually related to an underlying disease (e.g. autoimmune disorders, aggressive lymphomas, infections).

Cold agglutinin disease is rare. A population based study of cold agglutinin disease suggested a prevalence of 16.2 cases per million and incidence rate of 1.0 cold agglutinin disease per million per year (Norwegian population) (Berensten et al 2006). The risk of cold agglutinin disease increases with age and the median age at diagnosis is 72 years (range 43, 91) (Swiecicki 2013). Cold agglutinin disease affects men and women in equal proportions however the slight preponderance in women in some studies is likely due to women living longer than men.

Cold agglutinin disease severity can fluctuate and the thermal amplitude of the cold agglutinins is the most clinically relevant feature in determining disease severity. The degree of anemia is associated with substantial impairment in quality of life. Patients with cold agglutinin disease have symptoms of acrocyanosis, fatigue, dyspnea, hemoglobinuria, weakness, and weight loss. Special precautions have to be taken for the patient with cold agglutinin disease in order to avoid the consequences of exposure to cold temperatures. Extreme caution has to be taken in patients who undergo hypothermic surgical procedures, space heaters are often necessary to keep rooms at adequate levels, and intravenous solutions and previously refrigerated blood products must have temperature raised prior to infusion. Cooling blankets in patients with cold agglutinin disease with a fever are contraindicated as they can worsen hemolysis as well as peripheral gangrene.

There are no FDA approved therapies for the treatment of cold agglutinin disease. Nonpharmacological measures such as avoidance of cold temperature are effective in only a few mild cases. The use of splenectomy is not recommended since hemolysis in cold agglutinin disease occurs outside of the spleen. Supportive transfusions can be used in patients with severe anemia but cold agglutinin antibodies often complicate crossmatch because agglutination causes difficulty in detecting blood type and alloantibodies. The rate of transfusions in patients with cold agglutinin disease ranges from ~ 60-100% based on a review of the literature.

Other therapies that have been used to treat cold agglutinin disease include corticosteroids with responses ~ 7-14% and currently steroids are no longer recommended for the treatment of primary cold agglutinin disease. Rituximab has been used with response rates of ~ 57% and duration of response of 6-11 months (Reynaud et al 2015). Combinations of chemotherapy and rituximab (fludarabine) have been reported in the literature with 76% response rates and median duration of response of 66 months (Berensten et al 2010). There are also case reports for the treatment of primary cold agglutinin disease with bortezomib and eculizumab with varying degrees of success.

TNT009 is a humanized IgG4 monoclonal antibody that binds to and inhibits the classical complement pathway, specific serine protease, C1s, thus inhibiting complement activity. By binding to and inhibiting C1s, TNT009 prevents the enzymatic action of the C1 complex on its substrates, complement factors C4 and C2, thereby blocks formation of the C3 convertase. TNT009 only blocks the classical pathway leaving the alternative and complement-lectin pathway available for immune surveillance. TNT009 through inhibition of complement pathway could inhibit cold agglutination mediated complement destruction of RBCs obviating the need for transfusion in patients with cold agglutinin disease with severe anemia or transfusion dependence.

TNT009 was granted orphan designation for the treatment of autoimmune hemolytic anemia on July 27, 2016. IND 128190 was submitted to FDA on December 19, 2016.

7. Information related to endpoints used in the available clinical data:

a. Endpoints considered by the Sponsor as supporting breakthrough therapy designation include transfusion independence and increase in hemoglobin ≥ 4g/dL from baseline.

b. Endpoints accepted by the Division as a clinically significant endpoint(outcome measure) for patients with the disease:

- Transfusion independence
- Increase in Hgb ≥ 4g/dL

c. Any other biomarkers the division would consider likely to predict a clinical benefit event if not yet a basis for accelerated approval.

- No

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no available therapies for the treatment of primary cold agglutinin disease.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

None.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The breakthrough therapy designation request is based solely from Cohort C of the Sponsors Phase 1 /2 study.
Table 1: Summary of Clinical Data to Support Breakthrough Therapy Designation Request

Study	Phase	Cold Agglutinin Disease Population(Cohort C)	Number of Subjects in Cohort C	Endpoints
TNT009-01	Phase 1	Patients with primary CAD with Hgb Level < 11.0g/dL within 3 months preceding enrollment and at screening visit. Subjects excluded if prior treatment with systemic immunosuppressive agents, corticosteroids > 10mg prednisone, eculizumab or rituximab in previous 3 months	6 subjects enrolled with primary CAD	Transfusion independence and improvement in Hemoglobin(≥ 4g/dL)

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Study TNT009-01 is a prospective, double-blind, randomized, placebo-controlled first-in-human study of TNT009. The study is comprised of thee subparts: Part A, single ascending dose in normal healthy volunteers, Part B multi-ascending dose in normal healthy volunteers and Part C a multi-dose study in patients with complement mediated disorders including cohorts of patients with cold agglutinin disease, warm AIHA, bullous pemphigoid, and antibody mediated rejection in kidney transplant. The data from the 6 patients with primary cold agglutinin disease enrolled in Part C provides the primary basis for determination of breakthrough therapy designation. The population included patients with primary cold agglutinin disease with hemoglobin levels < 11.0g/dL within 3 months preceding enrolment and at screening visit. Subjects were excluded if prior treatments for cold agglutinin disease within prior 3 months.

The primary efficacy endpoints were transfusion independence and improvement in hemoglobin compared to baseline (≥4g/dL).

The dose schedule is 10mg/kg IV as initial test dose followed by 60mg/kg for four weekly doses. There was a washout period (3-4 weeks) and patients were allowed to continue on treatment in a Named Patient Program at dose of 5.5g IV every 2 weeks.

A total of 6 patients (all female) were enrolled in Part C of the study. Median age was 72 years (range 55, 76). At study entry 5 patients had transfusion dependent disease and 1 patient was transfusion independent. The median hemoglobin at baseline was 7.5g/dL (range 6.8, 8.2) and the median number of prior therapies was 2(range 2.6). Three of the 6 patients had history of prior thrombotic events.

Table 1 Baseline Demographics and Disease Characteristics in Study

Demographics and Exposure	**N=6**
Female	6(100%)
Median age	72(55,76)
Median baseline hemoglobin(g/dL)	7.5(6.8, 8.2)
RBC units in previous 12m, median	8 (2+, 52)
Median number prior therapies	2(2,6)
Median duration of TNT009 treatment	4 months(2, 12+)
Ongoing treatment	4(67%)

Efficacy results are presented for the 6 patients. The following table describes the efficacy results for patients with primary cold agglutinin disease on Study TNT009-01.

Table 2: Efficacy Response

Subjects	**Transfusion Independent after Initial Dosing**	**Hgb increase ≥4g/dL**	**Transfusion independence after TNT009 washout and retreatment**
5 transfusion dependent	100%	100%	100%
1 transfusion independent	Remained transfusion independent	100%	Remained transfusion independent

The median hemoglobin at baseline was 7.5g/dL and median hemoglobin after 4 doses of TNT009 was 11.8 g/dL(10.3, 13.2g/dL). The maximum hemoglobin increment in the first 7 weeks was + 4.2g/dL(range 1.7. 5.0). Dosing has continued up to 13 months(range 2-13). The patients who continued on treatment remained transfusion free with median Hgb values of 12.2g/dL(range of 11.6 to 13.2). Two patients discontinued continued treatment(one due to personal reasons and the second due to undiagnosed gynecological cancer).

Effect of TNT009 on Disease-Related Biomarkers: Circulating C1s, the molecular target of TNT009, was reduced to < 10% of pre-dose levels after TNT009 administration in the 6 CAD patients and returned to predose levels after the TNT009 washout. As a result, serum CH50 activity was inhibited by TNT009 for duration of treatment. Elevated serum bilirubin normalized or decreased within first 24 hours of TNT009 dosing and became elevated again during the washout. Haptoglobin was below the level of quantification in all the patients with primary cold agglutinin disease prior to TNT009 dosing and normalized in 4 of the 5 patients in which haptoglobin could be evaluated during course of study(not confounded by ex -vivo sample hemolysis and agglutination).

Effect of TNT on Functional or Symptomatic Improvement: Tachycardia, dyspnea and fatigue improved for the patients with CAD treated with TNT0009. One patient was able strong enough to go skiing again and one patient was able to resume walking and care for herself.

Summary of Preliminary Clinical Efficacy for TNT009 in subjects with Cold Agglutinin Disease:

- **Transfusion independence was observed in 5/5(100%) of patients who were transfusion dependent at baseline**
- **Hemoglobin increase of > 4g/dL was observed in all 6 patients**
- **Cessation of chronic hemolysis with improvement in clinical symptoms**
- **Responses sustained for 4 patients who continued treatment in continuation treatment program**

Safety Data: In the entire TNT009 development program, 30 patients have received TNT009. The most commonly reported adverse events were related to the common cold or headaches. There were no withdrawals due to adverse events.

Table 3: Safety Data for TNT009

Adverse Events	**Primary CAD N=6 N(%)**	**Total(All cohorts) N=30**
TEAE	5(83%)	27(90%)
Grade 5	0	1(3%)
Grade 4	0	0
Grade 3	0	0
Grade 1 or 2	5(83%)	26
SAEs	1(17%)	2(7%)

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT : Grant Breakthrough Designation for " Treatment of hemolysis in patients with primary cold agglutinin disease."

Rationale: Primary cold agglutinin disease is a rare and serious condition and substantial clinical evidence demonstrates an improvement in hemoglobin by ≥ 4g/dL and attainment of transfusion independence in 100% of patients with

transfusion dependence at baseline. The demonstration of improvement in hemoglobin and transfusion independence in a cohort of patients that have been heavily pretreated represents a meaningful clinical benefit for which no available therapy exists.

☐DENY:

Provide brief summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

Sponsor's plan: The Sponsor submitted an EOP 2 meeting request to discuss a proposed single-arm, multi-center pivotal study in patients with transfusion dependent primary cold agglutinin disease. The Sponsor plans to enroll ~20 patients with a primary endpoint of the number of patients who do not receive transfusions after first 5 weeks of study drug administration and who have Hgb levels increase from baseline of ≥ 2g/dL or absolute Hgb level≥12g/dL.

The Division acknowledges that single arm trial may be acceptable for approval for patients with cold agglutinin disease given rarity of disease and that approximately 20 patients would be reasonable number to evaluate.

13. List references, if any:

Berentsen S. How I manage cold agglutinin disease. Br J Haematol 2011; 153:309

Berentsen S. Ulvestad E Langholm R, et al. Primary chronic cold agglutinin disease: a population based clinical study of 86 patients: Haematological 2006; 91:460.

Berentsen S, Ulvestad E, Gjertsen BT, et al. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. Blood 2004:103:2925.

Brodsky, R.A. Complement in hemolytic anemia: Am J Hematol 2015: 126(22)" 2459-2465.

Gertz MA. Management of cold hemolytic syndrome. Br J Haematol 2007; 138:422.

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Swiecicki PL, Hegerova LT, Gertz MA. Cold Agglutinin disease. Blood 2013; 122(7):1114.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

4-6-15/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TANYA M WROBLEWSKI
05/15/2017

ROMEO A DE CLARO
05/16/2017

ANN T FARRELL
05/16/2017